Monoquaternary Neuromuscular Blocking Agents Based on 1-Tetralone and 1-Indanone

D. F. Biggs,* A. F. Casy, Ih Chu, and R. T. Coutts

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton T6G 2H7, Canada.
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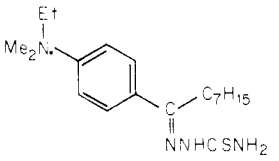
The preparation of three isomeric 1-tetralone hydrazones 4 and three isomeric 1-indanone hydrazones **5** possessing a single quaternary ammonium center is described. Several of the compounds possessed significant neuromuscular blocking activity, and two approached suxamethonium in potency. ^{1}H NMR evidence obtained from a study of the *N,N*-dimethylhydrazones indicated that the hydrazones adopted an *E* configuration in solution.

Some neuromuscular blocking agents based on *p*-dimethylaminophenyl alkyl ketones and 6-dimethylamino-1-tetralone, which have potencies comparable with that of suxamethonium in some species, have recently been reported.[1,2] These compounds, typified by the heptyl ketone thiosemicarbazone **1**[1] and the 1-tetralone hydrazone **2**,[2] possess a single quaternary ammonium center. The



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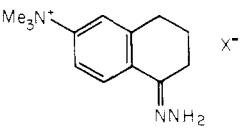

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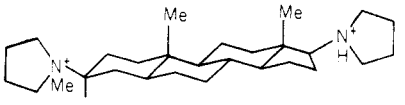
potent neuromuscular blocking agents (+)-tubocurarine[3,4] and the androstane **3**[5] are also monoquaternary derivatives but possess, in addition, a protonated nitrogen function. The cyclic skeletons of these compounds restrict the distance between the two nitrogen centers to a narrow range. If the quaternary group and the nitrogen function used to derivatize the carbonyl group in 1 and **2** are complementary, in the same sense as the quaternary and tertiary nitrogen substituents of (+)-tubocurarine and **3** (activity of **3** is lost when both nitrogens are tertiary or when the 17-substituent is replaced by C=O or OH),[5] then the potencies of 1, **2**, and their analogs should be sensitive to variations in the distance between the two nitrogen features of the molecules. To provide evidence on this point, the synthesis and pharmacological evaluation of the dimethylamino-1-tetralone **4** and 1-indanone **5** hydrazone



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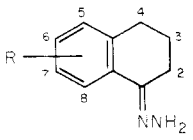
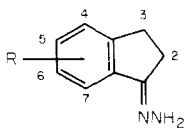
methiodides have been undertaken since these derivatives provide a wide range of quaternary nitrogen to hydrazone nitrogen separations.



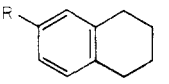
4a, R = 5-$^+$NMe$_3$
b, R = 6-$^+$NMe$_3$
c, R = 7-$^+$NMe$_3$



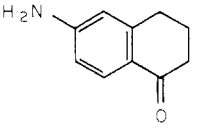
5a, R = 4-$^+$NMe$_3$
b, R = 5-$^+$NMe$_3$
c, R = 6-$^+$NMe$_3$

Most syntheses of the required hydrazones were achieved from previously described substituted tetralins or indans. Substituent orientation in these intermediates, originally established by conversions to analogs of known structure, e.g., 3(7)-nitro-1-tetralone to 1,3(7)-diaminonaphthalene,[6] was verified by means of ^{1}H NMR data.

6-Dimethylamino-1-tetralone hydrazone methiodide (**4b**) was prepared from 6-amino-1-tetralone (**7**) by N-methylation followed by reaction of the quaternary salt with hydrazine. The intermediate **7** was obtained from tetralin via the methyl ketone **6a**, oxime **6b**, and acetamide **6c**. The *N,N*-dimethyl analog of **4b** was similarly prepared from N-methylated **7** using 1,1-dimethylhydrazine. The 7-$^+$NMe$_3$ isomer **4c** was prepared by cyclization of 4-*p*-



6a, R = MeCO
b, R = MeC=NOH
c, R = MeCONH



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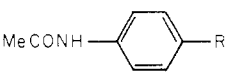
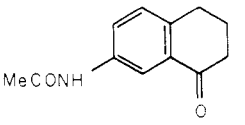
acetamidophenylbutyric acid (**8b**) with concentrated sulfuric acid to give 7-acetamido-1-tetralone (**9**). The precursor **8b** was obtained by catalytic reduction of the acid **8a** formed by a Friedel–Crafts reaction between acetanilide and succinic anhydride. The acetamide **9** was



8a, R = CO(CH$_2$)$_2$CO$_2$H
b, R = (CH$_2$)$_3$CO$_2$H



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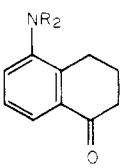
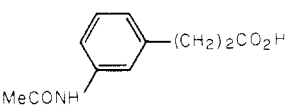
converted to the hydrazone **4c**, as in the synthesis of **4b**. The 5-$^+$NMe$_3$ isomer **4a** could not be prepared via an acetamido intermediate as in the 6-$^+$NMe$_3$ series, because 5-acetamidotetralin was resistant to oxidants. However, oxidation of 5-nitrotetralin (containing some of the 6-isomer) yielded a mixture of 5-, 6-, and 8-nitro-1-tetralones in low yield which was resolved by fractional crystallization and column chromatography. 5-Aminotetralone was derived by reduction with HCl–$SnCl_2$–$FeSO_4$. Resistance of both 5-amino-1-tetralone (**10a**) and the dimethylamino analog **10b** (obtained by reductive methylation of 5-nitro-1-tetralone)[7] to reaction with methyl iodide was observed. A quaternary salt was finally obtained by fusing **10b** with methyl tosylate and this salt was converted to the hydrazone **4a** (X^- = *p*-Me-C_6H_4-SO_3^-) as usual.



10a, R = H
b, R = Me



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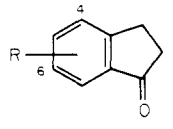
5-Dimethylamino-1-indanone hydrazone methiodide (**5b**) was prepared by cyclization of the acid chloride of *m*-acetamidohydrocinnamic acid (**11**) with $AlCl_3$. This gave a mixture of 5- and 7-acetamido-1-indanone in a 40:1 ratio. The major isomer was converted to **5b** by the usual

Table I. Activity of Hydrazones in the Cat in Vivo and on the Frog Rectus Muscle in Vitro and Their $^{+}NMe_3$ to NNH_2 Separations

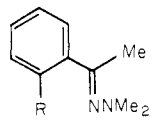
Compd[a]	Cat tibialis muscle prepn		Frog rectus abdominis muscle prepn[d]		
	ED_{50}, mmol/kg × 10^{-3}[b]	D_{50}, min[c]	Agonist act. (AcCh = 1000)	Antagonist act., affinity constant × 10^4	$^{+}NMe_3$ to NNH_2 distance, pm[e]
Suxamethonium	0.10 ± 0.007 (7)	4.4 ± 0.65			
4b	0.16 ± 0.002 (4)	5.2 ± 1.2	230 ± 26.5 (4)		790[f]
4a	>10		<2		740
4c	>10		<2	6.4 ± 0.7 (4)	650
5b	0.44 ± 0.042 (4)	10.0 ± 1.58	182 ± 16.6 (4)		810
5a	>10		<2		720
5c	3.98 ± 0.23 (4)	17.1 ± 2.5	27 ± 2.3 (4)		690
N,N-Dimethyl analog of **4b**	>10		<2		790
Gallamine triethiodide				36.0 ± 1.1 (3)	

[a] All iodides except suxamethonium (Cl^-) and **4a** ($MeTs^-$). [b] Dose ± standard error which caused 50% blockade of muscle twitches, figure in parentheses is the number of determinations. [c] Duration of action of an ED_{50} dose. [d] Figure in parentheses is the number of determinations. [e] Magnitudes ± 10 pm, measured from Dreiding models assuming an *E* configuration and a half-chair conformation for the alicyclic ring of the tetralones (that of the indanones is almost rigid and coplanar with the aromatic ring). [f] 620 pm for the *Z* configuration.

methods. The precursor acid 11 was obtained by the catalytic reduction of methyl *m*-nitrocinnamate followed by N-acetylation and acid hydrolysis. The 4-$^{+}NMe_3$ **5a** and 6-$^{+}NMe_3$ **5c** isomers were obtained by nitration of 1-indanone. The mixture of 4- and 6-nitro-1-indanone obtained was fractionally crystallized from hexane (monitored by ^1H NMR spectroscopy) and the 6-nitro isomer (major) was converted directly to 6-dimethylamino-1-indanone by catalytic reduction in the presence of formaldehyde; the tertiary base **12a** formed the quaternary hydrazone **5c** as usual. 4-Dimethylamino-1-indanone was isolated from a 1:1 mixture of 4- and 6-nitro-1-indanone after similar reductive methylation and was also converted to the corresponding hydrazone methiodide **5a**.



12a, R = 6-NMe_2
b, R = 4-NMe_2



13, R = H, OMe, Me, Br, Cl
δ_{NMe_2} 2.50–2.52
(2.25–2.31 for *Z* isomers)[8]

Results and Discussion

The pharmacological results are given in Table I. Several of the hydrazones (**4b**, **5b**, and **5c**) were significantly active as neuromuscular blocking agents and two approached suxamethonium in potency. Comparisons of the active hydrazones with suxamethonium rather than tubocurarine are valid because their mode of action was established as depolarizing blockade by the failure of the anticholinesterase, edrophonium, to reverse their effects in the cat and their agonist activity on the frog rectus muscle. The potency rankings of the hydrazones in the cat and frog muscle tests were similar, but the 7-dimethylaminotetralin **4c** was atypical in being inactive in the cat and an antagonist of AcCh on the frog rectus muscle.

The neuromuscular blocking potencies of the hydrazones **4** and **5** should be a function of the relative disposition of the trimethylamino and hydrazone groups since this is the only major variable within the two series. In this respect, the distance between the quaternary nitrogen and the amino nitrogen of the hydrazone function ($C{=}NNH_2$) is considered to be a more significant parameter than the Me_3N^+ to $N{=}C$ distance because all the active derivatives of 6-dimethylamino-1-tetralone methiodide are formed from reagents of the type H_2NNRR', the oxime analog, for example, being inactive.[2]

In the absence of ortho substitutents, the *E* (anti Ar/NH_2) configuration, with a half-chair alicyclic ring in the case of the tetralin derivatives, is the most probable stereochemistry of the hydrazones **4** and **5** because this geometry allows maximum resonance stabilization and minimum nonbonded interactions.[8] No ^1H NMR evidence about the hydrazone configuration was available because resonance signals of protons adjacent to the $C{=}NN$ unit were not well resolved. However, ^1H NMR spectra of the *N,N*-dimethylhydrazone methiodides of *p*-dimethylaminoacetophenone and 6-dimethylamino-1-tetralone showed single NMe_2 signals indicative of configurational purity and with chemical shifts close to those of the derivatives **13**, assigned *E* configurations.[8] Distance measurements were therefore made assuming an *E* configuration and are recorded in Table I. The Me_3N^+–NNH_2 distances for the two most active hydrazones, **4b** and **5b**, were 800 ± 10 pm, an N–N separation close to that found in potent derivatives based on *p*-dimethylaminophenyl alkyl ketones.[2] The N–N parameters of the hydrazones **4a**, **4c**, and **5a**, compounds all at least 100 times less potent than suxamethonium, fall in the range 650–740 pm. The value for the 6-dimethylamino-1-tetralone **5c** is anomalous since this compound is significantly more active than the three inactive compounds mentioned above. The activity of **5c** and the inactivity of **4a**, **4c**, and **5b** make it difficult to draw meaningful conclusions on the importance of Me_3N^+–NNH_2 distance in determining activity. It is apparent, however, that optimal activity is found when the two nitrogen-containing functions are separated by the maximal possible distance in both the indanone and tetralone series.

It is noteworthy that the hydrazones **4** and **5** cannot achieve significant populations of doubly charged species, comparable with those of suxamethonium or decamethonium, because the function $C{=}NNH_2$ is such a feeble base (the pK_a of **4b** is 2.5 in water, uncorrected for hydrolysis) that it is virtually unprotonated at physiological pH. The hydrazone group does, however, have electronegative character as a result of contributions from the resonance form 14[21] which may be sufficient to permit binding to an electron-rich site on the receptor. The marked fall in neuromuscular blocking activity that follows

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N,N-dimethylation of the hydrazone **4b** is probably steric in origin rather than the result of an increase in the basicity of the hydrazone functions since the change in pK_a is small (1–2 units).

Experimental Section

When analyses are indicated, analytical results obtained for those elements were within ±0.4% of the theoretical values. Melting points (uncorrected) were taken in a Thomas-Hoover capillary apparatus. Beckman IR-10 and Varian A-60D spectrophotometers were used to record ir and ^1H NMR spectra, respectively. Satisfactory spectral data were obtained for all compounds and generally only details of special relevance are given. ^1H NMR chemical shifts are given in parts per million (δ scale) with a Me_4Si standard and the abbreviations s (singlet), d (doublet), dd (doublet of doublets), t (triplet), and m (multiplet) are used. Reported δ and J values are mostly approximate since first-order analyses have been assumed.

6-Dimethylamino-1-tetralone Hydrazone Methiodide (4b). 6-Acetyltetralin, bp 96–100° (0.07 mm) [lit.[9] bp 132.5–134.5° (3.5–4 mm)], gave an oxime **6b**, mp 103–104° from hexane (lit.[9] mp 105–106°), which was rearranged to the acetamide **6c**, mp 105–106° from ligroine (lit.[10] mp 106–107°), by HAc–HCl[9] in 90% yield ($PhSO_2Cl$–Py[10] gave a 40% yield). Oxidation of **6c** with CrO_3–HAc–Ac_2O gave 6-acetamido-1-tetralone [mp 123–125° (lit.[11] mp 124–125°); ^1H NMR ($CDCl_3$) 8.0 (d, J = 8 Hz, H-8), 7.75 (d, J = 2 Hz, H-5), 7.4 (dd, J = 2, 8 Hz, H-7)] which was hydrolyzed to the amine **7**, mp 129–130° (lit.[11] mp 129.5–130°), by 6 N HCl. A mixture of **7** (4.8 g, 0.03 mol), MeI (20 g, 0.14 mol), Na_2CO_3 (2.0 g, 0.2 mol), and H_2O (30 ml) was heated under reflux for 48 h. The solvent was evaporated and the EtOH-soluble component of the residue recrystallized from EtOH–Et_2O to give 6-dimethylamino-1-tetralone methiodide (3.6 g, 36%), mp 147–148.5° (lit.[2] mp 147–148°). This methiodide (1.65 g, 0.005 mol) was treated with hydrazine (0.47 g, 0.015 mol) in EtOH (25 ml) for 3 h at reflux; the solvent was then evaporated and the residue recrystallized from EtOH–Et_2O to give the hydrazone methiodide **4b** (X = I^-), mp 189–191° (see ref 2).

7-Dimethylamino-1-tetralone Hydrazone Methiodide (4c). A mixture of 3-(*p*-acetamidobenzoyl)propionic acid (**8a**, 4.7 g), mp 196–197° (lit.[12] mp 202–205°) (aromatic ^1H NMR signal centered at δ 7.85 typically A_2B_2), 10% Pd/C (0.5 g), and MeOH (120 ml) was stirred with H_2 at room temperature and atmospheric pressure until about 1.2 l. of gas absorbed. The product was filtered, the filtrate evaporated, and the crude Me ester of **8b** (4 g, ν_{max} 1735 cm^{-1}) heated with 15% NaOH–H_2O (30 ml) on a steam bath for 15 min and then poured on ice. The solution was acidified with 6 N HCl and the precipitate recrystallized from EtOAc–Et_2CO to give 4-(*p*-acetamidophenyl)butyric acid (**8b**), mp 172–174° (lit.[13] mp 174–175°). A solution of the acid **8b** (8 g) in concentrated H_2SO_4 (60 ml) was heated at 80° (oil bath) for 16 h, then cooled, and poured on ice to give 7-acetamido-1-tetralone (**9**, 4.5 g): mp 162–164° (lit.[14] mp 165–166°); ^1H NMR (Me_2SO-d_6) 8.14 (d, J = 2 Hz, H-8), 7.86 (dd, J = 2, 8.5 Hz, H-6), 7.42 (d, J = 8.5 Hz, H-5). Cyclization of **8b** with $POCl_3$ or the corresponding acid chloride with $AlCl_3$ failed; 4-(*p*-acetamidophenyl)butyryl chloride (3 g, 62%), mp 90.5–93° from Et_2O–petroleum ether (bp 30–60°), was obtained by stirring a mixture of the acid **8b** (4.4 g, 0.02 mol), $SOCl_2$ (4.5 g, 0.04 mol), Na_2CO_3 (5 g, 0.5 mol), and C_6H_6 (20 ml) for 4 h. Anal. ($C_{12}H_{14}ClNO_2$) C, H, N. A mixture of **9** (4.8 g) and 6 N HCl (30 ml) was heated under reflux for 3 hr, then cooled, and made alkaline to give 7-amino-1-tetralone (3.8 g, 95%), mp 135–137° from C_6H_6 (lit.[14] mp 137°). A mixture of the aminotetralone (2.8 g, 0.02 mol), MeI (20 g, 0.14 mol), Na_2CO_3 (2 g, 0.2 mol), and H_2O (30 ml) was heated under reflux for 48 h and then more MeI (10 g, 0.07 mol) and Na_2CO_3 (2 g, 0.2 mol) were added. After a further 24-h reflux, the solvent was evaporated and the residue (freed from inorganic salts by extraction with EtOH) recrystallized from MeOH to give 7-dimethylamino-1-tetralone methiodide (4 g, 60%), mp 203–204°. Anal. ($C_{13}H_{18}INO$) C, H, N. It gave a hydrazone **4c** (X = I^-), mp 160–162°, formed as described for **4b** except that a 24-h reflux was required. Anal. ($C_{13}H_{20}IN_3$) C, H, N.

Nitro-1-tetralones. Nitration of tetralin (132 g)[15] gave a mixture of 5- and 6-nitrotetralin (137 g), bp 160–170° (23 mm), which was fractionated (Vigreux column) to yield (1) 5-nitrotetralin (20 g) [bp 88–92° (0.06 mm); mp 32° (lit.[15] mp 34°); ^1H NMR spectrum (CCl_4) similar to that of 3-nitro-o-xylene]; (2) a mixture of isomers (70 g) [bp 92–94° (0.06 mm)]; and (3) a mixture enriched in 6-nitro isomer (30 g) [bp 94–98° (0.06 mm) [lit.[15] bp 169° (13 mm)]; ^1H NMR spectrum (CCl_4) similar to that of 4-nitro-o-xylene]. CrO_3 (80 g) was added to a stirred mixture of 5-nitrotetralin (plus 6-isomer impurity) (100 g) and AcOH (400 ml) at 70–80° (steam bath) during 45 min and the temperature held for a further 2 h. An excess of CrO_3 was decomposed with MeOH (10 ml) and the solvents were evaporated in vacuo. The residue in Et_2O (300 ml) was washed successively with H_2O, 5% $NaHCO_3$–H_2O, and H_2O; then the Et_2O was dried and evaporated, and unreacted nitrotetralin (58 g) was distilled at 100–105° (0.15 mm). The residue was fractionally crystallized from ligroine to give a mixture of nitrotetralones (9.5 g, 8.4%) from which was separated 5-nitro-1-tetralone (2.3 g): mp 98–102° (lit.[16] mp 103–104°); ^1H NMR ($CDCl_3$) 7.39 (t, J = 8 Hz, H-7), 8.0 (dd, J = 1.5, 8 Hz, H-6 or 8), 8.25 (dd, J = 1.5, 8 Hz, H-6 or 8). The mother liquors were chromatographed on alumina (500 g, Alcoa heated at 120° for 6 h and deactivated with 15 ml of H_2O) and eluted with petroleum ether (bp 30–60°)–$CHCl_3$. When the $CHCl_3$ content was 25%, three fractions were obtained: (1) 5-nitro-1-tetralone (0.5 g); (2) 6-nitro-1-tetralone (0.1 g) [mp 102–104° (lit.[16] mp 105°) depressed by 7- and 8-nitro isomers; ^1H NMR ($CDCl_3$) 8.06 (s, 3-ArH)]; and (3) 8-nitro-1-tetralone (1.0 g) [mp 147–150° (lit.[16] mp 153–154°); ^1H NMR ($CDCl_3$) 7.33 (m, 3-ArH)]. 7-Nitro-1-tetralone, mp 105–106° (lit.[6] mp 106°), was obtained from 1-tetralone by the procedure used to nitrate 1-indanone.[17]

5-Dimethylamino-1-tetralone Hydrazone (10b). 5-Amino-1-tetralone, mp 119–120° (see ref 16), obtained by reduction of 5-nitro-1-tetralone was resistant to methylation by MeI, Me_2SO_4, and CH_2O–HCO_2H. The tertiary amine **10b** was obtained by stirring a mixture of 5-nitro-1-tetralone (2.1 g), CH_2O–H_2O (6 ml, 37%), EtOH (50 ml), and 10% Pd/C (0.5 g) with H_2 at room temperature and atmospheric pressure until about 1.2 l. of gas absorbed. The product was filtered, the filtrate evaporated, and the residue recrystallized from petroleum ether (bp 30–60°) to give 5-dimethylamino-1-tetralone (1.4 g): mp 60–62°; ν_{max} 1693 cm^{-1}; ^1H NMR ($CDCl_3$) 2.28 and 2.80 (m, 6 aliphatic H), 2.72 (s, NMe_2), 7.52 (m, 3-ArH). Fusion of **10b** (0.5 g, 0.003 mol) and methyl tosylate (0.5 g, 0.003 mol) at steam bath temperature for 96 h under N_2 gave **5-dimethylamino-1-tetralone methyl tosylate** (0.8 g, 70%), mp 194–195° from EtOH. Anal. ($C_{20}H_{25}NO_4S$) C, H, N. It formed a hydrazone **4a** (X = *p*-$MeC_6H_4SO_3^-$), mp 140–142°, from EtOH–Et_2O as usual. Anal. ($C_{20}H_{27}N_3O_3S$) C, H, N.

5-Dimethylamino-1-indanone Hydrazone Methiodide (5b, X = I^-). A mixture of methyl *m*-nitrocinnamate (62 g), mp 124–125° (lit.[18] mp 123–124°), 10% Pd/C (3 g), and EtOAc (1 l.) was stirred with H_2 at room temperature and atmospheric pressure until about 27 l. of gas had been absorbed. The product was filtered and the filtrate evaporated to give **methyl *m*-aminohydrocinnamate** (49 g, 92%), mp 116–118° (0.25 mm). Anal. ($C_{10}H_{13}NO_2$) C, H, N. AcCl (20.3 g, 0.26 mol) was added to a stirred mixture of the Me ester (47 g, 0.26 mol), NEt_3 (26 g, 0.26 mol), and C_6H_6 (700 ml) which was then heated under reflux for 1 h, then cooled, and filtered. The filtrate was evaporated to give **methyl *m*-acetamidohydrocinnamate** (58 g, 99%), mp 79.5–81° from Et_2CO–hexane. Anal. ($C_{12}H_{15}NO_3$) C, H, N. A mixture of the amide (21 g, 0.1 mol) and 15% NaOH–H_2O (120 ml) was heated with stirring on a steam bath for 5–10 min until a solution formed. Ice followed by excess of 20% HCl was added and the precipitate was crystallized from EtOH to give ***m*-acetamidohydrocinnamic acid** (11), mp 162° (see ref 18). $SOCl_2$ (11.8 g, 0.1 mol) was added to a stirred mixture of the acid 11 (16 g, 0.08 mol), Na_2CO_3 (8 g, 0.08 mol), and CH_2Cl_2 (240 ml), the product was then stirred for 3 h, and the supernatant was decanted and concentrated. Fresh CH_2Cl_2 (200 ml) was added to the residue followed by $AlCl_3$ (16 g). The mixture was stirred 4 h, then poured on ice, and extracted with $CHCl_3$. The dried extract was evaporated leaving a mixture of 5- and 7-acet-

amido-1-indanones (6 g, 36%) which was fractionally crystallized from EtOH to give **5-acetamido-1-indanone** (2 g) [mp 167–168°; ν_{max} 1695, 1605 cm^{-1}; ^{1}H NMR (Me_2SO-d_6), 7.75 (2 H), 7.93 (1 H) (2 br s, 3-ArH). Anal. ($C_{11}H_{11}NO_2$) C, H, N] and the **7-acetamido isomer** (0.05 g) [mp 105–110°; ν_{max} 1675, 1605 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) 7.08 (d, J = 8 Hz, H-4), 7.62 (t, J = 8 Hz, H-5), 7.83 (d, J = 8 Hz, H-6). Anal. ($C_{11}H_{11}NO_2$) C, H, N]. A mixture of 5-amino-1-indanone (1.7 g), mp 184–186° from EtOH [Anal. (C_9H_9NO) C, H, N], obtained by hydrolysis of the acetamide as usual, CH_2O–H_2O (6 ml, 37%), MeOH (50 ml), and 5% Pd/C (0.5 g) was stirred with H_2 at room temperature and atmospheric pressure until about 0.5 l. of gas was absorbed. The product was filtered, the filtrate evaporated, and the residue stirred with MeI (10 ml) and Et_2CO (20 ml) for 48 h to give **5-dimethylamino-1-indanone methiodide** (1.5 g), mp 154–156° from MeOH–EtOH. Anal. ($C_{12}H_{16}INO$) C, H, N. It formed a **hydrazone 5b** (X = I$^-$), mp 164–166°, from MeOH–H_2O as usual. Anal. ($C_{12}H_{18}IN_3$) C, H.

4- and 6-Dimethylamino-1-indanone Hydrazones. 1-Indanone (12 g), bp 94° (0.1 mm), mp 37–38° (lit.[18] mp 42°) (prepared by Koo's method),[19] was nitrated[17] to give a mixture of nitroindanones (12.5 g) which was extracted with successive quantities of hexane (300 ml, 67–70°). The first and second extracts contained a 1:1 mixture of 4- and 6-nitro-1-indanone (6 g) [^{1}H NMR ($CDCl_3$) 3.32 (m, H-3 protons of 6-isomer), 3.67 (m, H-3 protons of 4-isomer)], while the residue from the rest (6 g, chiefly one isomer) was crystallized to give 6-nitro-1-indanone: mp 71–74° (lit.[17] mp 74°); ^{1}H NMR ($CDCl_3$) 3.32 (m, H-3 protons). This isomer was converted to the tertiary amine **12a**, mp 78–80° [Anal. ($C_{11}H_{13}NO$) C, H, N], as described for the 5-dimethylamino analog. It formed a **methiodide**, mp 232–233° from MeOH [Anal. ($C_{12}H_{16}INO$) C, H, N], and a **hydrazone methiodide 5c** (X = I$^-$), mp 180–182° from MeOH [Anal. ($C_{12}H_{18}IN_3$) C, H], by usual methods (12-h reflux with hydrazine). A 1:1 mixture of 4- and 6-nitro-1-indanone (8 g) was reductively methylated as earlier described. Fractional crystallization of the product from hexane (67–70°) and Et_2CO gave the 6-dimethylamino isomer (6 g) while mother liquors contained the oily 4-isomer (3 g): ^{1}H NMR ($CDCl_3$) 2.85 (s, NMe_2), 2.88 (m, aliphatic H), 7.18 (m, ArH). Anal. ($C_{11}H_{13}NO$) C, H, N. The latter formed a **methiodide**, mp 232–235° from MeOH [Anal. ($C_{12}H_{16}INO$) C, H, N], and a **hydrazone methiodide 5a** (X = I$^-$), mp 197–199° from MeOH [Anal. ($C_{12}H_{16}IN_3$) C, H, N] as usual.

***N,N*-Dimethylhydrazones.** A mixture of 6-dimethylamino-1-tetralone methiodide (1.6 g, 0.005 mol), 1,1-dimethylhydrazine (0.6 g, 0.01 mol), HAc (0.6 g), and EtOH was heated under reflux for 3 h. The solvent was evaporated and the residue crystallized from EtOH–MeOH to give **6-dimethylamino-1-tetralone *N,N*-dimethylhydrazone methiodide** (1.2 g, 64%): mp 177–178°; ^{1}H NMR (Me_2SO-d_6), 2.58 (s, NMe_2), 3.71 (s, NMe_3). Anal. ($C_{15}H_{24}IN_3$) C, H, N. Similar treatment of *p*-dimethylaminoacetophenone methiodide, mp 182–183° (lit.[2] mp 185–187°), gave the corresponding ***N,N*-dimethylhydrazone**: mp 168–169°; ^{1}H NMR (Me_2SO-d_6) 2.47 (s, ArMe), 2.72 (s, NMe_2), 3.89 (s, NMe_3). Anal. ($C_{13}H_{22}IN_3$) C, H, N.

Pharmacological Methods. 1. Cat Sciatic Nerve–Tibialis Muscle Preparation. The methods of Bamford et al.[5] were used to determine potency, duration of action, and mechanism of action. **2. Frog Rectus Abdominis Muscle Preparation.** The methods used were essentially those published by the Edinburgh staff.[20]

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